EXPLORING THE LINK BETWEEN GASTRIC MOTILITY AND INTRAGASTRIC DRUG DISTRIBUTION IN MAN

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ABSTRACT

In drug development, the stomach is often considered to be a simple, one-compartmental organ, a waiting room for transfer of an orally administered dosage form to the duodenum. However, factors such as gastric acidity and hydrodynamics in the gastric environment may influence drug disposition. Although a link between gastrointestinal drug behaviour and gastric motility has often been hypothesized, they have not been simultaneously investigated in humans yet. In this proof-of-concept study, the combination of a well-established intraluminal sampling technique with high-resolution manometric measurements in the gastrointestinal tract was evaluated. This new combination of *in vivo* techniques proved to be feasible from a practical point of view and yielded valuable additional information regarding intraluminal drug behaviour. As a first application, the link between fasted state gastric motility and (in)homogeneous distribution of an orally administered drug in the stomach was investigated in healthy subjects. To this end, drug concentrations were measured in different regions of the stomach after oral administration of a commercially available drug product (Gabbroral®, 250 mg paromomycin) during a specific period of gastric contractile activity. A clear trend towards better mixing of an orally administered drug with gastric contents was observed when dosed in the presence of gastric contractions, resulting in a more homogeneous distribution of the drug throughout the stomach compared to dosing in the absence of gastric contractions.

KEYWORDS

Gastrointestinal, motility, oral drug delivery, drug distribution, biopharmaceutics, stomach, clinical trial

ABBREVIATIONS

MMC	Migrating Motor Complex
TIM	TNO Intestinal Model
9-fluorenylmethoxy-carbonyl chloride	Fmoc-Cl
C_{max}	Maximal drug concentration
f_{sim}	average similarity factor
MRI	Magnetic Resonance Imaging

1. INTRODUCTION

After oral administration, most drugs travel along the gastrointestinal tract to eventually be absorbed at the level of the small and/or large intestine. Before reaching these sites of absorption, a drug first has to migrate through several other sites (e.g. oral cavity, oesophagus and stomach). As passage through the mouth and oesophagus occurs rapidly, the stomach is typically the first compartment in which a drug resides for a longer period of time [1-3].

Although several anatomical regions in the stomach have since long been identified [4, 5], these are seldom recognized in drug development. When evaluating drugs and formulations, the stomach is often considered to be a simple, one-compartmental organ in which a drug awaits transfer to the duodenum relatively undisturbed. This is illustrated by the fact that most *in vitro* dissolution tools use a single vessel to mimic the gastric environment and only account for the acidity of the stomach, hereby neglecting other gastric physiological factors that potentially affect drug disposition. For instance, hydrodynamics are often introduced in these systems by means of stirring bars, creating fluid flow patterns which are not at all representative for the *in vivo* situation [6, 7]. By oversimplifying the dynamic gastric environment regarding motility, processes such as dosage form disintegration, drug - gastric fluid mixing and gastric emptying may be incorrectly simulated in *in vitro* systems.

Gastric motor function is characterized by predominant tonic contractions in the proximal region and peristaltic contractions in the distal region of the stomach [8]. Peristaltic contractions originate in the midcorpus region and migrate towards the pylorus, meanwhile increasing in both amplitude and velocity [9]. During the interdigestive state, periods of contractile quiescence alternate periods of contractile activity in a continuous cycle called the *'Migrating Motor Complex (MMC)'* [10, 11]. Generally, this cyclical pattern consists of three phases. The absence of contractions is characteristic for MMC phase I. Moderate peristaltic contractions (mean: 39.7 ± 14.4 mmHg; n = 40) with irregular frequency mark the beginning of MMC phase II activity. As phase II transitions into phase III activity, the amplitude of these contractions further increases (mean: 88 ± 31.7 mmHg) [12]. MMC phase III can either originate in the stomach or the small intestine. In the stomach, this phase is generally of short duration (2 - 6 min) and is characterized by a regular contraction frequency (2 - 3

contractions.min^{-1}) [11, 12]. Although marked variation within and between subjects has been observed, mean duration of one MMC cycle is often reported to range between 1.5 and 2 hours [12-16].

As the presence, amplitude and frequency of gastric contractions under fasted state conditions fluctuates in a time-dependent manner, an orally administered drug may exhibit variable behaviour (e.g. disintegration, distribution) depending on the time of administration relative to the MMC phase. Although gastrointestinal motility itself has been the subject of extensive research efforts, both in animal species and humans, the direct link between motility and drug disposition can still be considered mainly uncharted territory [9, 10, 17-19]. In recent years, wireless motility capsule studies have yielded important information regarding biorelevant pressures exerted on non-disintegrating dosage forms and their relation to gastric emptying [20-22]. Furthermore, some work has been performed to visualize tablet erosion in the stomach due to mixing of the dosage form with gastric contents [23]. Efforts have been made to translate the *in vivo* obtained data to *in vitro* predictive tools to be used during drug development, in order to better reflect *in vivo* gastric motility (e.g. dynamic gastric model, TIM-advanced gastric compartment) [24-27]. Nevertheless, a clear need still exists to better understand fundamental drug disposition processes such as dosage form disintegration and drug distribution in relation to gastric motor function. Although the link between drug behaviour and gastric motility has often been hypothesized, it has not been demonstrated *in vivo* so far. To this end, this study assessed the feasibility of combining intraluminal sampling of gastrointestinal fluids after oral drug administration, a well-established approach to elucidate gastrointestinal drug behaviour [28], with simultaneous motility measurements. As a first application of this new combination of *in vivo* techniques, the link between fasted state gastric motility and (in)homogeneous distribution of an orally administered drug in the stomach was investigated in healthy subjects.

2. MATERIALS AND METHODS

2.1. Chemicals

Paromomycin sulfate, glycine and 9-fluorenylmethoxy-carbonyl chloride (Fmoc-Cl) were purchased from Sigma-Aldrich (Diegem, Belgium). Boric acid was acquired via Acros Organics (99.5%, for analysis; Geel, Belgium). Chem-Lab (Zedelgem, Belgium) supplied acetic acid, while sodium acetate trihydrate ($NaOAc.3H_2O$) was ordered from VWR (Leuven, Belgium). Acetonitrile and methanol were purchased from Fisher Scientific (HPLC grade; Leicestershire, UK) and Acros Organics (HPLC grade; Geel, Belgium), respectively. Purified water for analytical purposes was obtained using a Maxima system (Elga Ltd., High Wycombe Bucks, UK).

2.2. Clinical trials

2.2.1. Clinical trial approval

Clinical trials followed the tenets of the Declaration of Helsinki and were approved by the Federal Agency for Medicines and Health Products (FAMHP; EudraCT reference number 2013-000297-30) and the Medical Ethics Committee of the University Hospitals Leuven (ML9149).

2.2.2. Clinical trial medication

Clinical trial medication, i.e. Gabbroral® (250 mg paromomycin; Pfizer, New York City, NY, USA), was ordered via the hospital pharmacy of the University Hospitals of Leuven (UZ Leuven, Belgium).

2.2.3. Preliminary clinical trial

In a pilot study with healthy human volunteers, gastric fluids were collected from different regions of the stomach, i.e. corpus and antrum, as a function of time at predetermined time-points after oral administration of one tablet of Gabbroral® (250 mg paromomycin) with 240 mL of tap water. Gastric fluids were aspirated using the well-established intraluminal sampling technique [28]. This technique comprises the positioning of double-lumen catheters (Salem Sump™ PVC Gastroduodenal Tube, 14

Ch (4.7 mm) x 108 cm; Covidien, Dublin, Ireland) via nose and/or mouth in a region of interest in the gastrointestinal tract using fluoroscopic guidance. Subsequently, gastrointestinal contents can be aspirated as a function of time providing valuable information regarding intraluminal drug disposition [29-32].

2.2.4. Clinical trial investigating drug distribution

Based on results obtained from the preliminary clinical trial, a cross-over trial was conducted including eight healthy volunteers (6 males, 2 females; age range: 20 - 26 years old). Candidate subjects were excluded from participation in case of (potential) pregnancy, frequent exposure to ionizing radiation in the previous year, history of gastrointestinal pathology and/or illness at the time of the study. Furthermore, Hepatitis B/C- or HIV-infected subjects were not allowed to participate in order to ensure the safety of the personnel conducting the study.

Volunteers were asked to refrain from eating and only consume water 12 hours prior to the start of the study in order to ensure fasted state conditions. After providing written informed consent the day of the study, double-lumen catheters were positioned in the corpus and antrum region of the stomach, respectively *(cfr. 2.2.3. Preliminary clinical trial)*. Additionally, a high-resolution manometry catheter (diameter 4.2 mm; Acertys, Aartselaar, Belgium) was introduced in the subject's duodenum via passage through the nose and the stomach. This catheter consists of 36 pressure sensors spaced 1 cm apart, providing the possibility of measuring regional pressures in both stomach and duodenum. By connecting the outer end of the catheter to a computer console, specialized computer software (Manoview Analysis™, version 2.0.1, Los Angeles, CA, USA) generates a high-resolution pressure map, facilitating real-time monitoring of pressure events and enabling drug administration during a specific phase of gastric contractions. Based on the generated high-resolution pressure map, quantification of the contraction amplitude is theoretically possible. However, due to limitations in the instrumentation available and as this study aimed to qualitatively assess the link between gastric motility and intragastric drug distribution, quantification was not pursued.

Following conditions were tested on different days with a minimum wash-out period of two days:

- Oral administration of one tablet of Gabbroral® (250 mg paromomycin) with 240 mL of tap water during MMC phase I (i.e. absence of contractions).
- Oral administration of one tablet of Gabbroral® (250 mg paromomycin) with 240 mL of tap water during MMC phase II (i.e. period of gastric contractions).

In both test conditions, gastric fluids were collected from both the corpus and antrum region of the stomach for three hours at predetermined time-points, i.e. 5, 15, 25, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170 and 180 minutes after oral drug administration (t_0). The volume of gastric aspirates was kept as small as possible (< 3 mL). Immediately after aspiration, samples were centrifuged (5 min, 20,817 x *g*; Microcentrifuge 5424, VWR International, Radnor, PA, USA) in order to separate liquid from solid material and obtain a homogeneous filtrate. Supernatant was subsequently filtered through a two-membrane filter system (Chromafil® GF/RC, pore size: 1.0/0.20 µm, diameter: 25 mm; Machery-Nagel, Düren, Germany). After discarding the first ten droplets for reasons of adsorption, filtrate was collected in a test tube and stored on ice. Subjects were asked to remain seated in a hospital bed (i.e. semi-supine position) and to not put any external pressure on their stomach (e.g. laptop) in order not to influence pressure measurements. After three hours of aspiration, the position of the catheters was checked again via fluoroscopy to ensure aspiration catheters had not markedly shifted position during the course of the experiment. At the end of the experiment, samples were frozen at -26°C pending analysis.

2.3. Sample analysis

In order to determine paromomycin concentrations in gastric aspirates, the compound was linked to a fluorophore (i.e. Fmoc-Cl) prior to analysis via a method adapted from Kumar et al. [33]. For this purpose, a mixture of 430 µL boric acid solution (24.7 $mg.mL^{-1}$ in H_2O, pH 8), 20 µL gastric aspirate

and 500 µL Fmoc-Cl solution (1.03 mg.mL^{-1} in acetonitrile) was thoroughly vortexed and stored protected from light to allow for the derivatization reaction to take place. After ten minutes, 50 µL glycine solution (7.5 mg.mL^{-1} in boric acid solution) was added to the mixture to stop the reaction. After a centrifugation step to separate dissolved material from precipitated protein content (5 min, 14000 *g*, 37°C; Eppendorf™ 5804R Centrifuge, Fischer Scientific, Leicestershire, UK), supernatant was transferred to a vial for analysis. Concentrations of the derivatization product were determined via reversed-phase HPLC (RP-HPLC) using a Waters 2695 Separations Module (Waters, Milford, MA, USA) and a Novapak C18 column under radial compression (pore size 60 Å, particle size 4 mm, 8 mm i.d. x 100 mm; Waters). The compound was isocratically eluted from the column at a flow rate of 1 mL.min^{-1} using a mixture of acetonitrile and H_2O (87:13, v/v), resulting in a retention time of eight minutes. After rinsing the column with methanol: acetic acid buffer (25 mM, pH 3.5) (75:25, v/v) and H_2O: acetic acid buffer (25 mM, pH 3.5) (75:25, v/v), the column was reconditioned with mobile phase. Eluent was detected using fluorescence detection at 260 nm (excitation) / 315 nm (emission) (Waters 2475 Multiwavelength Fluorescence Detector; Waters, Milford, MA, USA). The method was fully validated in relevant media within a linear range from 1300 to 10 µM, with all criteria meeting the FDA requirements for bio-analytical method validation.

2.4. Data interpretation

To assess the similarity between regional drug concentration-time profiles, a similarity factor ($f_{sim}(t)$) was calculated at each aspiration time-point *t* based on drug concentrations measured:

$$f_{sim}(t)\ (\%) = \left[1 - \frac{\left|[\text{drug}]_{\text{antrum (t)}} - [\text{drug}]_{\text{corpus (t)}}\right|}{[\text{drug}]_{\text{highest (t)}}}\right] \times 100$$

Subsequently, the average similarity factor (f_{sim}) was calculated as a measure of intragastric drug homogeneity, taking only into account similarity factors based on relevant drug concentrations (i.e. [drug] ≥ 5% of C_{max} for minimally one sampling region) to avoid skewing of results due to very low drug concentrations at later time-points:

$$f_{sim}(\%) = \frac{\sum_{t=1}^{n} f_{sim}(t)}{n} = \frac{f_1 + f_2 + \cdots + f_n}{n}$$

n = number of time-points per profile for which $f_{sim}(t)$ was calculated.

A non-parametric Wilcoxon test was performed to evaluate the statistical significance of the obtained data; differences between test conditions were considered statistically significant at $p > 0.05$.

3. RESULTS AND DISCUSSION

3.1. Preliminary findings on intragastric drug distribution

In a pilot study, regional drug concentrations were measured as a function of time in the stomach of healthy volunteers after oral administration of one tablet Gabbroral® (250 mg paromomycin) with water (*cfr. 2.2.3. Preliminary clinical trial*). Conflicting results regarding homogeneity of drug distribution in the stomach were obtained. For some volunteers, drug concentration-time profiles in corpus and antrum of the stomach compared reasonably well, whereas for others, regional drug concentrations measured were more inhomogeneous. Examples illustrating both scenarios are depicted in Figure 1. A possible explanation for the observed variability in drug distribution throughout the stomach could hypothetically be found in between-subject differences in gastric motor activity at the time of dosing. As fasted state gastric motility displays time-dependent fluctuations, it seems likely that also hydrodynamics in the stomach are prone to marked changes as a function of time. For example, mixing of gastric contents could be hypothesized to be more efficient during a period of gastric motor activity compared to a period without gastric contractions. As a result, drug distribution in the stomach may be affected by the MMC phase during which the drug is administered. According to this hypothesis, little or no mixing of gastric contents during MMC phase I administration would result in inhomogeneous distribution of a drug in the stomach, whereas dosing during MMC phase II/III would lead to more homogeneous drug distribution resulting from the adequate mixing of gastric contents. Since the pilot study did not provide any information regarding dosing relative to gastric motor activity, a second study was conducted to investigate this hypothesis.

3.2. Influence of gastric motor function on intragastric drug distribution

3.2.1. High resolution manometry to monitor gastrointestinal motility

A multitude of methods can be used to investigate gastrointestinal motility in healthy subjects and patients [9, 13, 20, 21, 34-37]. For several reasons, it was opted to use the high-resolution manometry technique in this study. From a practical point of view, the ease of use for the test operator was an important selection criterion. As a combination with the labour-intensive intraluminal sampling technique was strived for, the technique of choice should not add an additional burden on the test operator. Once correctly positioned, the high-resolution manometry catheter is connected to a computer console after which no additional interventions are required by the operator for the entire duration of the experiment. This allows the operator to perform additional actions such as blood sampling and aspiration of gastrointestinal fluids. This feature provides a clear advantage over other techniques sometimes used to investigate gastrointestinal motility (e.g. MRI, ultrasonography) which often require continuous hands-on presence of the test operator [36-38]. With regard to the tolerability of the manometry technique for study participants, intubation via the nose and positioning of the catheter may provide some temporary discomfort. However, the catheter is generally well-tolerated once correctly positioned. Importantly, alterations in gastrointestinal physiology (e.g. gastric emptying, gastric secretions) as a result of the intraluminal presence of a catheter have been reported to be negligible [39, 40].

Another important feature of the high-resolution manometry technique is the comprehensibility of the data output. Whereas several other techniques (e.g. ultrasonography, electrogastrography) require an expert in the field to interpret experimental data, the manometry technique produces a comprehensible output in the form of a high-resolution pressure map (Fig. 2) [36, 41]. This pressure map is colour-coded, with colours ranging from blue (no pressure) to pink (pressure > 150 mmHg). Based on the generated data, valuable information regarding regional gastrointestinal motor activity can be collected as a function of time. Distinct anatomical regions can easily be identified based on (i) basic knowledge

of gastrointestinal anatomy and (ii) well-described regional characteristics of gastrointestinal motility in literature. For example, the transition from oesophagus to stomach is easily distinguished by relatively high pressure events at the frequency of the subject's swallowing (Fig 2, section A), which can be attributed to the sphincter activity at the gastro-oesophageal junction. Secondly, as gastric contraction waves have been described to intensify towards the pylorus, corpus and antrum regions of the stomach can be differentiated based on the amplitude of registered contractions [9]. Furthermore, peristaltic contraction waves originate from midcorpus and subsequently propagate towards the antrum and pylorus, thus resulting in a small but distinguishable time-delay in onset of antral contractions compared to the corpus, providing a second identifier for both regions (Fig. 2, sections B and C). Substantial differences in both contraction frequency and amplitude between antrum and duodenum again allow reliable identification of both anatomical regions (Fig. 2, sections C and D) [11, 12].

Although both wireless motility capsules (e.g. IntelliCap®, SmartPill®) and the high-resolution manometry catheter record gastrointestinal pressures, the information gathered using these techniques markedly differs. Wireless motility capsules register regional gastrointestinal pressures as a function of time, however the region in which measurements are recorded varies as the capsule migrates along the gastrointestinal tract, rendering this technique useful to investigate pressures to which a solid dosage form is exposed during its transit [20-22]. On the other hand, high-resolution manometry provides simultaneous data on both gastric and proximal duodenal pressures as a function of time. Moreover, pressures are recorded from the same regions for the entire duration of the measurements. Although not pursued in the present study (*cfr. 2.2.4. Clinical trial investigating drug distribution*), quantifying the amplitude of gastrointestinal contractions *in vivo* may be useful for the further optimization of *in vitro* predictive tools to be used during drug development.

In the context of investigating gastrointestinal drug disposition, using the high-resolution manometry technique thus provides the opportunity to accurately determine gastric contractility at the time of oral dosing. In doing so, the influence of gastric motor function on drug distribution in the stomach could

be investigated in this study by orally administering a drug both in the presence and absence of gastric contractions.

3.2.2. (In)homogeneity of intragastric drug distribution

Similar as for the pilot study, homogeneity of intragastric drug distribution was assessed by collecting aspirates from different regions of the stomach as a function of time after oral intake of one tablet Gabbroral® (250 mg paromomycin) with water. In addition, gastrointestinal motility measurements were performed in parallel to facilitate drug administration during a specific MMC phase (*cfr. 2.2.4. Clinical trial investigating drug distribution*). Paromomycin, a BCS Class III drug, was chosen as a model compound to investigate drug distribution in the stomach of fasted healthy volunteers. Due to its high solubility within a wide pH range and its very low intestinal permeability, this compound has previously been used as a marker for gastrointestinal transfer of drug solutions [31]. In this study, a lack of solubility-restrictions throughout the gastrointestinal tract ensures the absence of interfering intraluminal processes (e.g. drug precipitation), facilitating the correct interpretation of regional drug concentrations measured in the stomach as a function of time. Furthermore, by comparing catheter position prior to and after the experiment, sampling of gastric contents in distinctly different regions of the stomach throughout the experiment was ensured (Fig. 3).

Figure 4 depicts the individual regional drug concentration-time profiles in all volunteers for both conditions tested in the clinical study. Based on these profiles, the similarity between concentrations measured in the antrum and corpus region of the stomach was calculated (*cfr. 2.4. Data interpretation)*. Regardless of gastric motor function at the time of dosing, similarity of regional drug concentration-time profiles was highly variable among volunteers (Fig. 5). Overall, f_{sim} values calculated ranged from 14.29 to 79.84%. A low f_{sim} value indicates inhomogeneous drug distribution in the stomach, whereas a high f_{sim} value suggests adequate mixing of gastric contents with an orally administered drug. The wide range of f_{sim} values observed in this study challenges the traditional thinking with regard to drug distribution. Rather than being rapidly distributed throughout the stomach

after dosage form disintegration, homogeneous intragastric drug distribution may in some cases be markedly hampered. With regard to the underlying mechanism determining intragastric drug distribution, a link between (in)homogeneity and fasted state gastric motility was observed in this study. With the model compound administered during a period of contractile quiescence (i.e. MMC phase I), median f_{sim} calculated from individual f_{sim} values for all healthy volunteers, amounted to 28.25% (Fig. 5). This finding supports the hypothesis regarding impaired mixing of gastric contents in the absence of gastric contractions. However, three healthy volunteers (V03, V06 and V08, Fig. 4 and 5) displayed remarkably better similarity between regional drug concentrations compared to the median f_{sim} for this group (63.8 - 75.24% vs. 28.25%, respectively); this indicates that, despite the absence of gastric contractions, drug distribution in the stomach may still be adequate in some cases. Drug administration in the presence of gastric contractions resulted in a median f_{sim} of 57.64% between regional concentration-time profiles. Comparing both test conditions, a trend towards more homogeneous drug distribution in the presence of gastric contractions can be deduced, as illustrated by a two-fold increase in median f_{sim} during phase II drug administration compared to phase I administration (57.64 vs. 28.25%, respectively; $p > 0.05$, NS). Additionally, it would have been interesting to investigate the inter-individual variability in contraction amplitude and how this may relate to differences observed in similarity of regional profiles.

Notably, drug administration in the presence of gastric motor activity does not automatically guarantee homogeneous intragastric drug distribution. The median value is in this case influenced by f_{sim} values which are lower than anticipated based on our hypothesis. These counterintuitive findings again point towards other factors influencing distribution of an orally administered drug in the stomach.

In the context of additional determinants of intragastric drug distribution, factors such as medium viscosity and site-specific dosage form disintegration may be considered. Several authors have performed *in vitro* experiments investigating the impact of changes in medium viscosity on dosage form disintegration and drug dissolution in an attempt to elucidate negative food effects for BCS Class I and III drugs [7, 42-44]. In all cases, disintegration and dissolution processes were found to be markedly delayed after addition of viscosity-enhancing agents to traditionally used buffer media.

Despite the fact that these experiments aimed to mimic changes in rheological properties of gastric fluids after food intake, the results may to some extent also apply to gastric fluids under fasted state conditions. Although viscosity of gastric contents is generally assumed to be significantly higher under fed state conditions, Pedersen et al. reported marked viscosity in several gastric aspirates from fasted healthy volunteers, in line with our in-house experience [45, 46]. As processes such as dosage form disintegration and dissolution are significantly affected by the viscosity of the medium, an impact of viscosity on drug distribution due to impaired diffusivity and increased resistance to fluid flow may be possible. This may in some cases result in localized drug release, even in the presence of gastric contractions. Stamatopoulos et al. further explored this hypothesis by visualizing fluid flow patterns and investigating their relation to mixing and drug distribution in an *in vitro* setup (USP 2 mini vessel). When medium viscosity was artificially increased, hydrodynamics markedly changed resulting in a worsening of fluid mixing compared to the reference medium. To investigate the subsequent impact on drug distribution, the authors performed dissolution experiments with theophylline tablets determining drug concentrations in samples taken from multiple sampling sites as a function of time. A marked difference in drug concentrations measured at different sites was observed as the viscosity of the medium increased [6]. Although the hydrodynamics in these experiments do not resemble the *in vivo* situation, results indicate that viscosity of gastric fluids may indeed contribute to inhomogeneous mixing of gastric contents. Using a video-endoscopic technique, Graham et al. attempted to visualize gastric dispersion of KCl crystals formulated as multiparticulate dosage forms (i.e. a capsule or a tablet) in healthy volunteers. Their findings suggest that these crystals may in some cases be regionally present in very high concentrations due to drug 'entrapment' in gastric mucus [47, 48].

A second factor potentially affecting intragastric drug distribution is the location of the administered dosage form within the stomach. For instance, Weitschies et al. reported marked variability in intragastric tablet location between subjects [49]. As contractility patterns and amplitude of contractions display site-specific characteristics (e.g. proximal corpus vs. antrum), forces acting on a dosage form may vary substantially depending on its intragastric location [8, 9, 50]. Therefore,

disintegration of a dosage form located in the proximal stomach may be less affected by intense antral contractions compared to dosage forms residing in the distal stomach [47, 49]. As a result, drug dispersion and distribution throughout the stomach may be hampered. Due to the fact that the study design did not allow to determine the location of the administered tablet within the stomach, a possible influence of between-subject differences in intragastric location of the dosage form could not be ruled out. Furthermore, although the position of the subjects during the experiment was standardized (i.e. semi-supine) in an attempt to cancel out differences in stomach shape and dosage form location due to posture (e.g. upright vs. supine), a multitude of variations in stomach anatomy have been previously reported, potentially influencing the results observed in this study [51].

4. CONCLUSIONS AND FUTURE PERSPECTIVES

In this proof-of-concept study, the feasibility of combining intraluminal sampling of gastrointestinal aspirates after oral drug administration with simultaneous recordings of gastrointestinal pressures via high-resolution manometry was explored. The high-resolution manometry technique is easy in use and well-tolerated by the study participants. Furthermore, the data output from this technique is comprehensible and provides valuable information regarding gastrointestinal motility in a time-dependent manner. Therefore, the combination with the intraluminal sampling of gastric fluids was found to be very useful to explore possible links between gastrointestinal motility and drug disposition.

In a first application, the influence of fasted state gastric motor function on intragastric drug distribution in healthy volunteers was investigated. A clear trend towards better mixing of an orally administered drug with gastric contents was observed in the presence of gastric contractions, resulting in a more homogeneous distribution of the drug throughout the stomach. Although a link between gastric motor function and drug distribution was established, several other factors may contribute to the intragastric dispersion and distribution of a drug (e.g. tablet location, medium viscosity). The results obtained in this study challenge the concept of the stomach as a simple dissolution vessel, as

similarity in regional drug concentrations displayed marked between-subject variability and was observed to be far from homogeneous in all test conditions. In the future, quantification of intraluminal pressures in a large set of both healthy volunteers and patients may be of interest as these data could be used as a reference for the further optimization of *in vitro* tools. Furthermore, more research is needed to investigate gastrointestinal motility as a source of variability in intraluminal processes such as dosage form disintegration and, eventually, in systemic drug exposure.

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Figure captions

Figure 1. Regional drug concentration-time profiles obtained from two volunteers in the pilot study after oral administration of one tablet Gabbroral® (250 mg paromomycin) with 240 mL tap water. ■ Regional drug concentrations measured in corpus region of the stomach as a function of time. ● Regional drug concentrations measured in antrum region of the stomach as a function of time.

Figure 2. Colour-coded high-resolution pressure map generated using high-resolution manometry, depicting typical late phase II/phase III gastrointestinal contractions. Colours range from blue to pink, indicating contraction amplitude. Distinct regions can be identified: A. Gastro-oesophageal junction, B. Corpus, C. Antrum, D. Duodenum.

Figure 3. Catheter position in a healthy volunteer at the beginning (a) and the end of the study (b), verified using fluoroscopic imaging. Aspiration catheters are positioned in corpus (A) and antrum (B) region of the stomach, respectively. The high-resolution manometry catheter can easily be distinguished by the dotted line, in which each dot represents an individual pressure channel.

Figure 4. Individual regional drug concentration-time profiles from all volunteers (n = 8) for both test conditions. ■ Drug concentrations measured in the corpus region of the stomach as a function of time. ● Drug concentrations measured in the antrum region of the stomach as a function of time.

Figure 5. Similarity of regional drug concentration-time profiles, expressed as f_{sim}, as a function of MMC phase during which a drug is administered. Cross-over nature of the study is illustrated by the use of a unique symbol for each volunteer. Horizontal lines depict median f_{sim} values in both test conditions.